IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA and REGENXBIO INC.,

Plaintiffs,

v.

SAREPTA THERAPEUTICS, INC. and SAREPTA THERAPEUTICS THREE, LLC,

Defendants

C.A. No. 20-1226 (RGA)

JURY TRIAL DEMAND

[redacted]

REDACTED

PLAINTIFFS' OPENING BRIEF IN SUPPORT OF THEIR MOTION FOR SUMMARY JUDGMENT OF NO INVALIDITY UNDER 35 U.S.C. § 101, MOTION FOR SUMMARY JUDGMENT THAT SAREPTA'S INFRINGING ACTIVITIES ARE NOT PROTECTED BY THE SAFE HARBOR OF 35 U.S.C. § 271(E)(1), *DAUBERT* MOTION TO PRECLUDE THE TESTIMONY OF DR. MARK KAY ON INVALIDITY UNDER 35 U.S.C. § 112, AND *DAUBERT* MOTION TO PRECLUDE THE TESTIMONY OF CARLA MULHERN ON HOLD-UP

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Plaintiffs' motions for summary judgment and *Daubert* motions are all based on a straightforward proposition—Sarepta should be held to this Court's prior rulings, established law, and admitted facts. At the outset of this case, this Court rejected Sarepta's argument that its infringing activities were protected from liability under the safe harbor of 35 U.S.C. § 271(e)(1), finding that "under *Proveris*, a patented product that is not subject to FDA premarket approval is not a 'patented invention' under § 271(e)(1)." (D.I. 66 at 2.) Despite establishing no new facts regarding its activities, Sarepta has continued to argue that its activities are protected by the safe harbor in contravention of that prior ruling. Similarly, at claim construction, this Court rejected Sarepta's argument that an "AAV . . . capsid protein" required specific functionality, instead adopting a "plain and ordinary meaning" construction for that term. (D.I. 118.) Ignoring the record of this case, Sarepta's expert now opines that the patents are invalid under 35 U.S.C. § 112 by asserting that the "plain and ordinary meaning" includes many of the same functionalities that this Court rejected during claim construction. The Court should hold Sarepta to its prior rulings on the safe harbor and claim construction, and reject Sarepta's contradictory arguments.

Sarepta also ignores controlling legal precedent on the test for patent eligible subject matter under 35 U.S.C. § 101 and on the requirements for establishing "hold-up" in its damages analysis. Sarepta's arguments for ineligibility under § 101 focus on only one element of the claims rather than each claim as a whole, as the law requires. Its experts have admitted that the subject matter recited by each claim as a whole—the cultured host cells with the required components—does not occur in nature, so there are no facts in dispute. Sarepta also ignores damages law and the facts in this case by having its expert opine that there was "hold-up" in this case that improperly increased the damages, even though "hold-up" is entirely inapplicable in this context and unsupported by the factual record.

Plaintiffs thus request that this Court grant their motions for summary judgment on the issues of safe harbor and patent eligibility, and their *Daubert* motions to exclude expert testimony under the wrong claim construction for § 112 and the wrong law for "hold-up."

I. NATURE AND STAGE OF THE PROCEEDINGS

Plaintiffs REGENXBIO Inc. and the Trustees of the University of Pennsylvania filed a Complaint against Defendants Sarepta Therapeutics, Inc. and Sarepta Therapeutics Three, LLC on September 15, 2020, accusing Sarepta of infringing U.S. Patent No. 10,526,617. Sarepta moved to dismiss, arguing that its actions were protected by the safe harbor. (D.I. 12.) The Court denied that motion on January 4, 2022, (D.I. 36), and denied Sarepta's motion for certification for interlocutory appeal on May 23, 2022, (D.I. 66 at 2). The Court held a claim construction hearing on December 20, 2022, issuing its claim construction order December 30.

Fact and expert discovery are now closed. A pretrial conference in this matter is set for January 19, 2024, and a five-day trial is scheduled to begin January 29, 2024.

II. MOTION FOR SUMMARY JUDGMENT THAT THE CLAIMS OF THE '617 PATENT ARE NOT PATENT INELIGIBLE UNDER 35 U.S.C. § 101

There is no dispute that the invention recited in the asserted claims—a cultured host cell containing a recombinant nucleic acid molecule with nucleic acid sequences from more than one organism—does not occur in nature. Sarepta's witnesses freely admitted this at deposition, and Sarepta has never disputed this point during the course of this litigation. These admissions alone end the inquiry under § 101; if a claim is not directed to one of the subject matter exceptions, here, a natural phenomenon, it is patent eligible at step one of the *Alice/Mayo* test; there is no need to move on to step two.

Sarepta argues that, even though the claimed invention is a product that undisputedly does not occur in nature, it is still ineligible under § 101. Sarepta makes this argument by

improperly focusing on a single element of the claims—the specific amino acid or nucleotide sequence recited by the claims, which is known as AAVrh.10. While the AAVrh.10 sequence on its own may occur in nature, the claimed invention requires that sequence be combined with a heterologous non-AAV sequence in a recombinant nucleic acid molecule that resides in a cultured host cell. All witnesses in this case agree that such cultured host cells do not occur in nature. Moreover, it is undisputed that the claimed cultured host cells have markedly different functions than the AAVrh.10 sequence alone. *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980); *Nat. Alternatives Int'l, Inc. v. Creative Compounds, LLC*, 918 F.3d 1338 (Fed. Cir. 2019). When the claims here are considered as a whole, as the law requires, they are plainly not directed to a natural phenomenon, and Plaintiffs' motion for summary judgment that the claims are not patent ineligible under 35 U.S.C. § 101 should be granted.

A. Summary of the Argument

1. The asserted claims of the '617 patent recite cultured host cells containing a recombinant nucleic acid molecule that comprises two parts—one that encodes the sequence of AAVrh.10 or a sequence at least 95% identical to that sequence, and one that includes a heterologous, non-AAV sequence. All witnesses agree that such cultured host cells do not exist in nature.

2. When looking at each asserted claim as a whole, as is required under step 1 of the *Alice/Mayo* test, there is no dispute that that subject matter—cultured host cells with the specific claim requirements—is not a natural phenomenon. Nor is there any dispute that the claimed cultured host cells are significantly different than a bare AAV sequence as a matter of function.

3. Sarepta's only argument to the contrary is that the claims are "directed to" a natural product and thus claim ineligible subject matter. This argument is improper and legally incorrect because it focuses only on one portion of the claim—the claimed sequences. Sarepta's analysis

is directly contrary to the requirement that, at step 1, "the claims are considered in their entirety to ascertain whether their character as a whole is directed to excluded subject matter." *McRO, Inc. v. Bandai Namco Games Am. Inc.*, 837 F.3d 1299, 1312 (Fed. Cir. 2015).

4. The Patent Office recognizes that, based on the precedent in *Alice* and *Mayo*, claims like the asserted claims, which recite a cultured host cell or vector that includes a natural sequence along with other features such as a heterologous non-AAV sequences, are eligible at step 1 because they are non-naturally occurring combinations that have markedly different functions that an AAV sequence alone. The Patent Office's analysis is consistent with governing precedent and on point for the asserted claims.

B. Statement of Facts

1. The Claims Recite Cultured Host Cells that Do Not Occur in Nature

Claim 1 of the '617 patent is representative. It recites:

> A cultured host cell containing a recombinant nucleic acid molecule encoding an AAV vp1 capsid protein having a sequence comprising amino acids 1 to 738 of SEQ ID No: 81 (AAVrh.10) or a sequence at least 95% identical to the full length of amino acids 1 to 738 of SEQ ID No: 81, wherein the recombinant nucleic acid molecule further comprises a heterologous non-AAV sequence.

(Ex. 1, '617 patent at claim 1.) The other independent claims of the '617 patent, claims 3, 5, and 7, are similar. Claims 3 and 5 are structurally the same as claim 1, but recite either vp2 or vp3 capsid protein sequences of AAVrh.10 in place of the vp1 capsid protein sequence recited in claim 1. (*Id*. at claims 3, 5.) Claim 7 contains similar claim elements to claims 1, 3, and 5, but recites the nucleotide sequences of AAVrh.10 in SEQ ID NO:59. (*Id*. at claim 7.)

The claims plainly do not claim only the sequence for the AAVrh.10 capsid protein. Instead, they claim cultured host cells containing a recombinant nucleic acid molecule which has at least two portions: one that encodes the sequence of AAVrh.10 (or a sequence at least 95% identical), and one that one that includes a heterologous, non-AAV sequence.

There is no dispute that the claimed cultured host cells are not products of nature. Sarepta's expert witnesses have uniformly admitted that the cultured host cells with the claimed features are not naturally occurring. When asked "Do the cultured host cells with the features required by the asserted claims exist in nature," Sarepta's expert Dr. Mark Kay unequivocally answered "No." (Ex. 2, Kay Tr. at 195:25-196:4.) And when asked if he would "agree that the cultured host cells claimed in the '617 patent are not naturally occurring," another Sarepta expert, Dr. Gabor Rubanyi, responded that "[m]y understanding about cultured host cells is that it's correct. It's not natural." (Ex. 3, Rubanyi Tr. at 250:24-251:21.)

Not only are the cultured host cells themselves not naturally occurring, there is no dispute that several features of the claimed cultured host cells are not naturally occurring. First, the claimed cultured host cells must include a recombinant nucleic acid molecule. "Recombinant" is typically understood to refer to a cell or organism with a combination of generic material from multiple sources. (Ex. 4, *Recombinant*, *Taber's Cyclopedic Medical Dictionary* (Taber's Online); Ex. 5, Leone Reb. Rpt. at ¶ 74.) And "recombinant DNA" refers to "[s]egments of DNA from one organism artificially manipulated or inserted into the DNA of another organism through gene splicing." (Ex. 6, *Recombinant DNA*, *Taber's Cyclopedic Medical Dictionary* (Taber's Online); Ex. 5, Leone Reb. Rpt. at ¶ 74.) Thus, a "recombinant" nucleic acid molecule refers to something that is "artificially" created, in other words, something that does not occur naturally.

Sarepta's own experts and employees agree that "recombinant" nucleic acids and cells containing them are not naturally occurring. When asked whether recombinant nucleic acids are "found in nature other than being engineered by genetic engineers or biologists," Dr. Kay answered "No." (Ex. 2, Kay Tr. at 193:1-17; *see also* Ex. 3, Rubanyi Tr. at 252:9-253:1

(agreeing that recombinant nucleic acid molecules are not naturally occurring).) Christopher Campbell, a Sarepta biologist, also admitted at his deposition that a recombinant mammalian cell line is not naturally occurring and that it is "accurate" that those cell lines "are created by scientists in a laboratory and don't exist in nature before the scientist created it." (Ex. 7, Campbell Tr. at 27:21-28:1; *see also id.* at 26:24-29:10 (agreeing that a "recombinant" mammalian cell line means a cell line that has been "genetically altered to produce the biological therapeutic").)

Second, the asserted claims require the recombinant nucleic acid in the cultured host cells contain a "heterologous non-AAV sequence," which also shows the claimed recombinant nucleic acid molecule cannot be naturally occurring. "Heterologous" is generally understood to mean coming from a different species, so the inclusion of a "heterologous non-AAV" sequence as part of the recombinant nucleic acid molecule in the claimed cultured host cells precludes those cells from being naturally occurring. By definition, they must include a recombinant nucleic acid that encodes an AAV capsid as well as a sequence from something other than AAV. Sarepta's expert, Dr. Rubanyi, agreed. (Ex. 3, Rubanyi Tr. at 252:20-253:1 ("Q. Would you agree that a recombinant nucleic acid molecule that contains an AAV sequence and a heterologous non-AAV sequence is not naturally occurring? . . . A. Yes, I agree." (objection omitted)).) There is thus no dispute of material fact that the combination of an AAV sequence with a heterologous non-AAV sequence is not a combination that occurs in nature, but instead must be created in a laboratory.

2. The Specification and File History Show that the Claims are Directed to Cultured Host Cells that Do Not Occur in Nature

The specification of the '617 patent explains that important discoveries the inventors made have led to significant advances in gene therapy. It discusses the novel methods that the inventors used to identify new AAV sequences with important, improved properties as compared

to the small number of previously known AAV sequences. The specification also highlights the important uses for those sequences. In particular, it discusses their use as being a part of the invention:

> [E]ach of these [AAV] fragments may be readily utilized in a variety of vector systems and host cells. Such fragments may be used alone, in combination with other AAV sequences or fragments, or in combination with elements from other AAV or non-AAV viral sequences. In one particularly desirable embodiment, a vector contains the AAV cap and/or rep sequences of the invention.

(Ex. 1, '617 patent at 3:49-56.) The specification also explains that that the claimed host cells and vectors that contain the newly discovered AAV sequences provide certain functional advantages, including for use in gene therapy:

> The invention further provides nucleic acid molecules, gene delivery vectors, and host cells which contain the AAV sequences of the invention. As described herein, the vectors of the invention containing the AAV capsid proteins of the invention are particularly well suited for use in applications in which the neutralizing antibodies diminish the effectiveness of other AAV serotype based vectors, as well as other viral vectors. The rAAV vectors of the invention are particularly advantageous in rAAV readministration and repeat gene therapy.

(*Id*. at 4:56-67; *see also id.* at 25:25-26.) The new AAV sequences on their own may be useful as primers and for sequence analysis, but they do not have the same utility as the host cells and vectors; it is only when combined with other components and used in a manner like the claimed inventions that the AAV sequences can be used in that manner. (Ex. 8, Leone Tr. at 128:20-129:13; Ex. 5, Leone Reb. Rpt. at ¶¶ 80-81.)

The file history also shows that the claims are directed to subject matter that does not occur in nature. After rejecting earlier versions of the claims that recited only "host cells" as directed to natural phenomena, the examiner dropped that rejection after the applicants amended the claims to require "cultured host cells." (Ex. 9, REGENX0006540-49 at REGENX0006543; Ex. 10, REGENX0006613-20 at REGENX0006614.) Thus, during prosecution of the '617

patent, the examiner recognized that the "cultured host cell" limitation overcame any section 101 concerns. "Cultured host cells" are created in a laboratory, using non-naturally occurring materials such as cell culture media. (Ex. 5, Leone Reb. Rpt. at ¶ 79.) These are not and cannot be cells that are simply isolated from a natural source, and no witness has suggested otherwise.

C. Legal Standards

"The court shall grant summary judgment if the movant shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a). If the non-moving party fails to make a sufficient showing on an essential element of its case with respect to which it has the burden of proof, the moving party is entitled to judgment as a matter of law. *See Celotex Corp. v. Catrett*, 477 U.S. 317, 322 (1986).

"Whether a claim is drawn to patent-eligible subject matter under § 101 is an issue of law." *In re Bilski*, 545 F.3d 943, 951 (Fed. Cir. 2008). Section 101 provides that "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." 35 U.S.C. § 101. Only three judicial exceptions for categories of subject matter that are not eligible for patentability exist—laws of nature, natural phenomena, and abstract ideas. *Alice Corp. Pty. v. CLS Bank Int'l*, 573 U.S. 208, 216 (2014).

Courts follow a two-step "framework for distinguishing patents that claim laws of nature, natural phenomena, and abstract ideas from those that claim patent-eligible applications of those concepts." *Alice*, 573 U.S. at 217; *see also Mayo Collaborative Servs. v. Prometheus Lab'ys, Inc.*, 566 U.S. 66, 77-78 (2012). At step one of the analysis, the Court determines whether the claims are directed to one of those three patent-ineligible concepts. *Alice*, 573 U.S. at 217. If the answer to that question is no, then "the claims satisfy § 101 and [the Court] need not proceed to the second step." *Core Wireless Licensing S.A.R.L. v. LG Elecs., Inc.*, 880 F.3d 1356, 1361 (Fed.

Cir. 2018). It is only if the Court finds that the claims are directed to a patent-ineligible concept that the Court must proceed to step two of the analysis. *Alice*, 573 U.S. at 217-18; *Mayo*, 566 U.S. at 72-73.

In the step one analysis, "the claims are considered in their entirety to ascertain whether their character as a whole is directed to excluded subject matter." *Internet Pats. Corp. v. Active Network, Inc.*, 790 F.3d 1343, 1346 (Fed. Cir. 2015). In doing this analysis, it is important not to oversimplify the claims or the claimed invention because all inventions, at least at some level, rely on abstract ideas, natural phenomena, or laws of nature. *Alice*, 573 U.S. at 217; *see also McRO*, 837 F.3d at 1313; *Enfish, LLC v. Microsoft Corp.*, 822 F.3d 1327, 1337-38 (Fed. Cir. 2016). "At step one, therefore, it is not enough to merely identify a patent-ineligible concept underlying the claim; [courts] must determine whether that patent-ineligible concept is what the claim is 'directed to.'" *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1050 (Fed. Cir. 2016). A claim to a composition of matter made from a natural product is not "directed to" the natural product where the recited composition has different characteristics and "the potential for significant utility." *See Chakrabarty*, 447 U.S. at 310.

D. Argument

1. The Asserted '617 Claims Are Not Directed to a Natural Phenomenon

There is no dispute between the parties that the asserted claims recite cultured host cells containing a recombinant nucleic acid molecule that encodes the sequence of AAVrh.10 (or a sequence at least 95% identical), and must also include a heterologous, non-AAV sequence. The entire claim—with all of the required elements—is the proper focus of the step 1 analysis for section 101 eligibility. *See McRO*, 837 F.3d at 1312 ("[T]he claims are considered in their entirety to ascertain whether their character as a whole is directed to excluded subject matter.").

Sarepta's experts have admitted that the claimed cultured host cells are not natural products. (*See* Ex. 2, Kay Tr. at 195:25-196:4; Ex. 3, Rubanyi Tr. at 250:24-251:21.) There is no dispute that the subject matter the claims are "directed to," i.e., the recited cultured host cells, are not a natural product and thus do not fall within one of the ineligible "exceptions" to section 101. Because the claims are plainly not directed to a natural product at step 1, summary judgment in favor of Plaintiffs is appropriate. *See Pac. Biosciences of Cal., Inc. v. Oxford Nanopore Techs., Inc.*, Nos. 17-0275-LPS-CJB, 17-1353-LPS-CJB, D.I. 447 at 12 (D. Del. Feb. 19, 2020) (attached as Ex. 27) ("Accordingly, Oxford cannot prevail even at step 1 of the *Alice* test, so summary judgment for PacBio on the subject matter eligibility of the '400 and '323 patents under § 101 is warranted."); *Pernix Ireland Pain DAC v. Alvogen Malta Operations, Ltd.*, No. 16-0139-WCB, 2018 WL2225113 at *24 (D. Del. May 15, 2018) (granting summary judgment of no invalidity under section 101 where claim was not directed to natural law).

2. The Claimed Cultured Host Cells Have Markedly Different Characteristics than the Sequences Themselves, Which Further Supports that they Are Not Naturally Occurring

That the claimed cultured host cells are not naturally occurring is supported by the fact that they have vastly different characteristics, function, and utility than the natural amino acid or nucleic acid sequences that encode AAVrh.10. *See Chakrabarty*, 447 U.S. at 309-10 (finding patent eligible a genetically engineered bacterium "with markedly different characteristics from any found in nature and one having the potential for significant utility"). While the amino acid and nucleotide sequences on their own may be used for sequence analysis or as primers, they are essentially "inert" and do not have additional, non-research functions. (Ex. 8, Leone Tr. at 121:21-122:16, 125:9-129:13; Ex. 5, Leone Reb. Rpt. at ¶¶ 80-81.) The claimed cultured host cells, however, are an integral part of the process to produce rAAV vectors for gene therapy. (Ex. 5, Leone Reb. Rpt. at ¶¶ 80-81; Ex. 8, Leone Tr. at 125:9-129:13.) The sequences alone

could not perform that function. The use of the cultured host cells as part of the process to make rAAV vectors for gene therapy is not a function that naturally occurring amino acid or nucleotide sequences of AAVrh.10 can do on their own. Sarepta has never asserted otherwise.

The facts here are similar to those in both *Chakrabarty* and *Natural Alternatives International, Inc. v. Creative Compounds, LLC*, 918 F.3d 1338 (Fed. Cir. 2019). In *Chakrabarty*, the Supreme Court found eligible claims to a genetically engineered bacterium "capable of breaking down multiple components of crude oil." 447 U.S. at 305, 318. No naturally occurring bacteria possessed the same property. *Id.* at 305. Thus, the "claim [was] not to a hitherto unknown natural phenomenon, but to a nonnaturally occurring manufacture or composition of matter—a product of human ingenuity having a distinctive name, character and use." *Id.* at 309-10 (cleaned up). The claims recited eligible subject matter because they reflected that "the patentee ha[d] produced a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility." *Id.* at 310.

And in *Natural Alternatives*, the product claims recited a human dietary supplement of beta-alanine, a naturally occurring compound, in unit dose form with a particular dose. The Federal Circuit overturned the district court's judgment on the pleadings that the claims were ineligible under section 101, finding that "[a]lthough beta-alanine is a natural product, the Product Claims are not directed to beta-alanine. A claim to a manufacture or composition of matter made from a natural product is not directed to the natural product where it has different characteristics and 'the potential for significant utility.'" 918 F.3d at 1348 (quoting *Chakrabarty*, 447 U.S. at 310). The Federal Circuit explained that the claimed supplements were

not products of nature because "they have different characteristics and can be used in a manner that beta-alanine as it appears in nature cannot." *Id.*

The same is true here. The claimed cultured host cells include components other than the AAV sequences themselves, and have different characteristics and utility in producing gene therapy vectors than the sequences alone. There is no dispute on this issue—Sarepta has never suggested that the natural AAV sequences can perform the same functions and be used in the manufacture of gene therapy vectors like the cultured host cells can.

3. Sarepta Raises No Factual Dispute on Whether the Claims Are Directed to a Natural Phenomenon

Sarepta has raised no factual dispute as to whether the claimed cultured host cells occur in nature; its experts have admitted that they do not. Instead, despite what the claims say, Sarepta argues that the are really "directed to" a single claim element—the natural AAVrh.10 sequence and related sequences. That argument is legally wrong. The proper inquiry for step 1 of the section 101 analysis is to look at the claims "as a whole," not to focus on one element of the claims to the exclusion of the others. *See McRO*, 837 F.3d at 1312. Sarepta's analysis ignores this law, and improperly focuses on a single element of the claims. Sarepta's expert, Dr. Kay admitted that the only basis for his step 1 analysis that the claims are directed to a natural phenomenon is that "the claim states rh10" and "we're talking about VP1 of rh10, which is a gene that occurs in nature." (Ex. 2, Kay Tr. at 203:25-206:5; *see also* Ex. 11, Kay Op. Rpt. at ¶ 127 ("At the most fundamental level, the claims are directed to amino acid and nucleic acid sequences encoding the capsid protein of the naturally occurring variant AAV rh.10 and other naturally occurring AAVs.").) Dr. Kay's analysis is exactly what courts have repeatedly rejected—arguing that a claim is directed to a natural product just because a natural product is part of the claim. *See Rapid Litig. Mgmt.*, 827 F.3d at 1050 (noting that, for the step one

analysis, "it is not enough to merely identify a patent-ineligible concept underlying the claim"); *Enfish*, 822 F.3d at 1337 (warning against "describing the claims at such a high level of abstraction and untethered from the language of the claims all but ensures that the exceptions to § 101 swallow the rule").

The claims of the '617 patent do not cover bare AAVrh.10 sequences. They recite a cultured host cell containing a recombinant nucleic acid molecule that encodes an AAV capsid protein comprising the required AAVrh.10 sequence and a heterologous non-AAV sequence. When examined as a whole, as the law requires, the claims of the '617 patent are not directed to a natural phenomenon.

4. The Patent Office's Guidelines for Section 101 Eligibility Demonstrate that the Asserted Claims are Directed to Eligible Subject Matter at Step 1

The Patent Office guidelines on section 101, issued after *Alice* and *Mayo*, further demonstrate that the '617 claims are not directed to a natural phenomenon and thus recite patent eligible subject matter. The Patent Office issued Interim Guidance on Subject Matter Eligibility in 2014 and again in 2015, including examples of how certain types of claims should be evaluated under section 101. The "nucleic acid" examples in the "Nature Based Product Examples" are particularly relevant here. Sample claim 1 recites "An isolated nucleic acid comprising SEQ ID NO: 1," and according to the Interim Guidance is ineligible because it simply recites a natural nucleic acid sequence. (Ex. 12, PTO Interim 101 Guidance, Nature Based Products and July 2015 Update Appendix 2: Index of Eligibility Examples at 10.) Sample claim 4, however, incorporates that natural sequence into a non-natural product, reciting "A vector comprising the nucleic acid of claim 1 and a heterologous nucleic acid sequence." (*Id.*) The Interim Guidance explains that sample claim 4 is *not* directed to a natural product at step 1 because "is limited to vectors comprising a non-natural combination of Gene W (SEQ ID NO: 1)

with a sequence from another organism, and thus does not read on the naturally occurring chromosome in Virginia nightshade." (*Id.* at 10-11, Example No. 15.) The Guidance also explains that the composition of claim 4 is both structurally and functionally different than the natural nucleic acid sequence:

> This non-natural combination results in the vectors having a different genetic structure and sequence than the naturally occurring nucleic acids, i.e., different structural characteristics. Some of the claimed vectors may have different functional characteristics, depending on the selected heterologous sequence. These differences rise to the level of a marked difference, and so the claimed vector is not a 'product of nature' exception.

(*Id.* at 11.)

The same is true here. As discussed in detail above, the claimed cultured host cells are structurally different from a bare AAV sequence, in that they require a recombinant nucleic acid that encodes the AAV capsid protein sequence and also includes a heterologous non-AAV sequence, all in a non-naturally occurring cultured host cell. And they are functionally different in a significant manner because of their utility as part of the process for making AAV vectors for gene therapy. The sequence alone, while it can be used for research, does not have that function.

E. Conclusion

For all the reasons above, Plaintiffs respectfully requests that the Court grant summary judgment that the asserted claims are not ineligible under 35 U.S.C. § 101.

III. MOTION FOR SUMMARY JUDGMENT THAT SAREPTA'S INFRINGING ACTIVITIES ARE NOT PROTECTED BY THE SAFE HARBOR OF 35 U.S.C. § 271(E)(1)

As explained in Plaintiff REGENXBIO's answering brief in response to Sarepta's Motion to Dismiss (D.I. 20), Sarepta's use of the claimed cultured host cells falls outside the statutory safe harbor of 35 U.S.C. § 271(e)(1). *Proveris Sci. Corp. v. Innovasystems, Inc.*, 536 F.3d 1256, 1265-66 (Fed. Cir. 2008). As the Court previously found, Sarepta does not make and

sell the cultured host cells. (D.I. 36 at 8-9; D.I. 66 at 2.) Instead, it makes and sells a gene therapy product, known as either SRP-9001 or ELEVIDYS. The patented cultured host cells are tools used during manufacturing of the product, and Sarepta does not need FDA premarket approval to make and use them.

These undisputed facts have not changed since the Court found Sarepta's use of the claimed cultured host cells is outside the safe harbor at the motion to dismiss stage. Plaintiffs' motion for summary judgment on this issue should be granted.

A. Summary of the Argument

1. Sarepta already argued that its accused activities were protected from infringement by the statutory safe harbor in its Motion to Dismiss, (D.I. 20), which this Court denied, (D.I. 36). Since then, Sarepta has not introduced any new facts to show that the patented cultured host cells are subject to FDA premarket approval—because they are not. The Court's findings in denying Sarepta's Motion to Dismiss are the "law of the case," and the Court should grant summary judgment for that reason alone.

2. No circumstances have changed and no new facts have been developed since Sarepta's Motion to Dismiss was denied. The controlling case law requires that to be within the statutory safe harbor, the patented invention must be subject to FDA premarket approval. There is no dispute in this case that the patented cultured host cells are not subject to FDA premarket approval, and Sarepta's arguments to the contrary do not apply the proper legal standard.

B. Statement of Facts

The process of making rAAV vector therapeutics such as Sarepta's SRP-9001 product (now commercially sold under the brand name ELEVIDYS) uses two types of "cultured host cells," both of which are alleged to infringe the '617 patent. (*See* D.I. 20 at 2-5.) Specifically,

rAAV vector products like Sarepta's therapeutic products are manufactured by [redacted] Sarepta has never denied that it uses [redacted] cultured host cells in this manner. [redacted]

The claims of the asserted '617 patent protect Plaintiffs' novel cultured host cell technology. Notably, the claims are not directed to a potential gene therapy treatment. For example, claim 1 recites:

> 1. A cultured host cell containing a recombinant nucleic acid molecule encoding an AAV vp1 capsid protein having a sequence comprising amino acids 1 to 738 of SEQ ID NO: 81 (AAVrh.10) or a sequence at least 95% identical to the full length of amino acids 1 to 738 of SEQ ID NO: 81, wherein the recombinant nucleic acid molecule further comprises a heterologous non-AAV sequence.

(Ex. 1, '617 Patent at claim 1.) The cultured host cells claimed in the '617 patent are tools Sarepta uses in its manufacturing process of its final gene therapy products, such as SRP-9001, and are consumed during this process. (Ex. 14, Leone Reply Rpt. at ¶ 6.)

While Sarepta's final gene therapy products require FDA premarket approval in order to be marketed and administered to patients—and in the case of SRP-9001 Sarepta has already received such approval—it is undisputed that the cultured host cells themselves used in the manufacturing process do not. (Ex. 15, Lietzan Reply Rpt. at ¶¶ 51, 57-58.) In fact, two of Sarepta's suppliers sell the cultured host cells to Sarepta—[redacted]

[redacted]. (Ex. 13, Leone Op. Rpt. at ¶¶ 295-297 [redacted] Neither of these third parties holds premarket approval from FDA directed to their cultured host cells, nor is FDA premarket approval required to market and sell them. (Ex. 15, Lietzan Reply Rpt. at ¶ 58.)

Sarepta's expert Ms. Sensabaugh opines that FDA guidance requires that information regarding Sarepta's use of cultured host cells in the manufacturing process of SRP-9001 be included in the regulatory approval application to FDA. (Ex. 16, Sensabaugh Reb. Rpt. at ¶ 72.) Plaintiffs have never disputed this fact. (Ex. 15, Lietzan Reply Rpt. at ¶¶ 53, 55-56.) While Ms. Sensabaugh opines that this means the cultured host cells are in fact "approved" by FDA, her opinion on this legal issue is inconsistent with the law and with this Court's prior rulings. (Ex. 16, Sensabaugh Reb. Rpt. at ¶ 70.) As this Court found, the cultured host cells themselves are not the subject of the application to FDA for premarket approval; the gene therapy product Sarepta sought a license to market and administer to patients is. (Ex. 15, Lietzan Reply Rpt. at ¶¶ 51, 57-58.) There is no factual dispute that under the correct legal standard, Sarepta's activities are not protected by the safe harbor, and summary judgment is appropriate here.

C. Argument

1. This Court Already Determined That Sarepta's Activities Were Not Protected by the Safe Harbor

When this Court denied Sarepta's Motion to Dismiss (D.I. 37), the question of whether Sarepta's activities were protected from allegations of infringement by the statutory safe harbor was decided for purposes of this action. In other words, the denial became the "law of the case." *See, e.g.*, *Arizona v. California*, 460 U.S. 605, 618 (1983), *decision supplemented*, 466 U.S. 144 (1984) ("[L]aw of the case . . . doctrine posits that when a court decides upon a rule of law, that

decision should continue to govern the same issues in subsequent stages in the same case."). The parties briefed this issue for the Court and argued their positions. This Court then held that "since the patented cultured host cells are not subject to FDA regulatory approval, they are not a 'patented invention' under § 271(e)(1)." (D.I. 36 at 8-9.) Sarepta moved to certify this issue for interlocutory appeal, which this Court denied as well. (D.I. 66 at 2 ("In denying the motion to dismiss, this Court held that under *Proveris,* a patented product that is not subject to FDA premarket approval is not a 'patented invention' under§ 271(e)(l).").) As discussed below, nothing in Sarepta's belated expert opinions concerning the safe harbor creates a factual dispute on this legal question. For this reason alone, summary judgment in Plaintiffs' favor is warranted.

2. There is No Dispute of Material Fact That Sarepta's Infringing Activities Fall Outside the Safe Harbor

a. Case Law Specifically Exempts Tools Like the Patented Cultured Host Cells from Safe Harbor

Section 271(e)(1) provides, *inter alia*, that it shall not be an act of infringement to use a "patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs . . . ." 35 U.S.C. § 271(e)(1). While the safe harbor provides broad protection for certain uses related to the "development and submission of information" to FDA, that protection is not limitless. "Despite the broad contours of the [safe harbor] exemption, some activities are outside its protection." *Momenta Pharms., Inc. v. Teva Pharms. USA Inc*., 809 F.3d 610, 619 (Fed. Cir. 2015) ("[R]esearch tools or devices that are not themselves subject to FDA approval may not be covered.") (citing *Proveris*, 536 F.3d at 1265-66).

The controlling decision discussing activities that fall outside the scope of the safe harbor is *Proveris*. There, the Federal Circuit held that the safe harbor did not apply to the use of a patented product in connection with FDA regulatory submissions, where, as here, the patented

product was not itself subject to FDA premarket approval. There, the plaintiff accused Innova of selling an Optical Spray Analyzer ("OSA") to companies that used the OSA solely to obtain data to support FDA approval of the final products. 536 F.3d at 1259. There was no dispute that the use of the OSA was solely related to activities directed to obtaining FDA approval. *Id*. Nonetheless, the Federal Circuit held that the OSA was outside the scope of the term "patented invention" in Section 271(e)(1). *Id*. at 1265-66. Since the accused OSA was not itself subject to premarket FDA approval, but rather only the product on which the tests were conducted needed such approval, the safe harbor did not apply. *Id*. at 1265 ("Innova's OSA device is not subject to FDA premarket approval . . . . [I]nsofar as its OSA device is concerned, Innova is not within the category of entities for whom the safe harbor provision was designed to provide relief.").

Moreover, the Federal Circuit noted that the asserted patent in *Proveris* was not eligible for Patent Term Extension ("PTE") under 35 U.S.C. § 156, and for that additional reason, the safe harbor did not apply. *Id*. at 1265-66 ("Because Proveris's patented product is not subject to a required FDCA approval process, it is not eligible for the benefit of the patent term extension afforded by 35 U.S.C. § 156(f).")

In reaching its decision, the *Proveris* court was guided by the Supreme Court's opinion in *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661 (1990). In reviewing the considerations leading to the Hatch-Waxman Act, the *Proveris* court noted how "sections 156 and 271(e)(1) were enacted in order to eliminate two unintended distortions of the effective patent term resulting from premarket approval required of certain products pursuant to the FDCA." *Proveris*, 536 F.3d at 1265 (citing *Eli Lilly*, 496 U.S. at 669-70). As the *Proveris* court understood, *Eli Lilly* explained that "the first distortion was the reduction of effective patent life caused by the FDA premarket approval process." *Id*. at 1265 (citing *Eli Lilly*, 496 U.S. at 669-70). This was

remedied by enactment of Section 156. The "second distortion was the de facto extension of effective patent life at the end of the patent term—also caused by the FDA premarket approval process." *Id*. (citing *Eli Lilly*, 496 U.S. at 669-70). This was remedied by enactment of Section 271(e)(1).

In reaching its conclusion that the OSA device in *Proveris* was not a "patented invention" as that term is used in Section 271(e)(1), the court noted that "in *Eli Lilly* the Court spoke of its interpreting the phrase 'patented invention' in section 271(e)(1) to include all products listed in section 156(f) [i.e., a drug product, medical device, food additive and color additive] as producing a 'perfect product fit' between the two provisions." *Id.* at 1265 (quoting *Eli Lilly*, 496 U.S. at 672). The *Proveris* court referred to this as a "symmetry" between the two provisions. *Id*. Since the OSA device was neither subject to premarket approval nor eligible for a patent term extension afforded by 35 U.S.C. § 156, it did "not need the safe harbor protection afforded by 35 U.S.C. § 271(e)(1)." *Id*. at 1266.

Since *Proveris*, district courts have followed its reasoning to find that alleged infringing products and tools that are not themselves subject to FDA premarket approval fall outside the protection of the safe harbor. For example in *PSN Ill., LLC v. Abbott Lab'ys*, No. 09-5879, 2011 WL 4442825 (N.D. Ill. Sept. 20, 2011), the asserted patents related to receptors that Abbott used to develop drug candidates that themselves required FDA premarket approval. Like the cultured host cells claimed in the '617 patent, the patented receptors in *PSN* were used by defendant Abbott to screen potential therapeutic agents, which did not themselves contain the patented receptor. *Id*. at *1-2. In holding that the safe harbor did not apply, the court relied on *Proveris*, and *Proveris's* analysis of *Eli Lilly* and the legislative intent behind Section 271(e)(1). *Id*. at *5-6. Since the patented receptors were not subject to FDA premarket approval, and "[defendants]

were using [them] to develop their own" product, the receptors were not a "patented invention" within the meaning of Section 271(e)(1). *Id*. at *6; *see also Isis Pharms., Inc. v. Santaris Pharma A/S Corp*., No. 11-2214, 2012 WL 4111157, at *5-6 (S.D. Cal. Sept. 18, 2012) (denying summary judgment of non-infringement and rejecting defendant's safe harbor defense because the patents-in-suit covered methods of modifying biologic molecules where only the final products, not the accused products, were subject to FDA premarket approval); *Allele Biotechnology & Pharms., Inc. v. Pfizer, Inc.*, No. 20-1958, 2021 WL 1749903, at *2, 6-7 (S.D. Cal. May 4, 2021) (denying motion to dismiss, finding that Allele's patented mNeonGreen product, "a fluorescent protein used as a biological tag in genetic engineering work," was not a "patented invention" under 35 U.S.C. § 271(e)(1), and therefore defendants' activities were outside the safe harbor).

Sarepta and its expert Ms. Sensabaugh ignore this relevant legal precedent. Ms. Sensabaugh did not address whether the patented cultured host cells are a "patented invention" within the scope of the safe harbor under *Proveris* or the cases following it. Instead, as discussed in further detail below, she provided opinions that information regarding the cultured host cells must be submitted to FDA as part of Sarepta's BLA, a point Plaintiffs have never disputed, and which is irrelevant to whether Sarepta's conduct is within the safe harbor.

b. The Patented Cultured Host Cells are Not Subject to FDA Premarket Approval

Like the patented OSA device in *Proveris*, the patented cultured host cells in this case are not subject to FDA premarket approval. Both parties agree that cultured host cells are used in the process of manufacturing Sarepta's gene therapy products and are not the final gene therapy products. Both parties also agree that information about the cultured host cells used in the gene therapy product manufacturing process is included as part of a BLA application, such as in

Sarepta's BLA application for its gene therapy product SRP-9001. (Ex. 15, Lietzan Reply Rpt. at ¶¶ 53, 55-56; Ex. 16, Sensabaugh Reb. Rpt. at ¶ 72.) However, Ms. Sensabaugh's opinion that the inclusion of this information means that the cultured host cells themselves are "FDA approved" is legally incorrect, and conflates the subject of a BLA to market and administer a biologic product with tools that are part of the manufacturing process. Indeed, Ms. Sensabaugh repeatedly opined, contrary to *Proveris*, *PSN Illinois*, *Isis Pharms*., and *Allele*, that all of the "manufacturing processes, facilities and equipment, and raw materials that are part of the BLA and inspected and approved by the FDA." (*See, e.g.*, Ex. 26, Sensabaugh Reply Rpt. at ¶ 20; *see also id*. at ¶¶ 22, 24-26, 29-31.) An argument like Ms. Sensabaugh's was expressly rejected in *Proveris*, with the Court finding that even though the patented device was "used by third parties solely for the development and submission of information to the FDA," that use was nevertheless not protected by the safe harbor. *Proveris*, 536 F.3d at 1260, 1266. Because Ms. Sensabaugh's view of what it means to be "FDA approved" is inconsistent with the controlling case law, as well as the law of this case, her opinions are irrelevant to the issues in this case and do not and cannot create an issue of fact that precludes summary judgment.

Ms. Sensabaugh's opinions do not address the correct legal question. Her opinions concern whether the cultured host cells used to manufacture Sarepta's gene therapy products are "subject to FDA regulatory approval," (*see, e.g.*, Ex. 16, Sensabaugh Reb. Rpt. at ¶ 20), and not whether "FDA premarket approval" is required. Whether FDA premarket approval is required or not is the correct inquiry, as this is the activity specifically discussed by *Proveris* in the reasoning regarding safe harbor. *See, e.g.*, 536 F.3d at 1265 ("Innova's OSA device is not subject to FDA premarket approval . . . . [I]nsofar as its OSA device is concerned, Innova is not within the category of entities for whom the safe harbor provision was designed to provide

relief."); *see also* Mem. Op. Denying Mot. to Dismiss (D.I. 36) at 8 ("I instead agree with REGENXBIO that *Proveris* holds that a patented product that is not subject to FDA premarket approval is not a 'patented invention' under § 271(e)(l)."). Ms. Sensabaugh failed to make this inquiry in her opinions. In fact, when asked about FDA premarket approval at her deposition, Ms. Sensabaugh could not even articulate what the term meant:

> Q: How does the term "subject to regulatory approval" that you used in your opinion differ from the term "premarket approval"?
>
> A: I would be answering off the top of my head if I answered your question. And I need to think more about it.
>
> Q: In conducting your analysis in this case and preparing your reports, you analyzed whether the accused cultured host cells are subject to regulatory approval and not whether they are subject to FDA premarket approval as the court used that term; is that correct?
>
> A: I was asked to review the BLA requirements and . . . how the host cells were part of the requirements of the BLA, the use of the host cells in manufacture in the BLA . . . . And I don't know what they mean when they say "premarket approval." I can only assume, and I don't want to make any assumptions. That would be speculation.

(Ex. 17, Sensabaugh Dep. Tr. at 53:24-54:23 (cleaned up).)

In contrast, Plaintiffs' expert Ms. Lietzan did the correct analysis: whether FDA premarket approval is required for the patented cultured host cells. (Ex. 15, Lietzan Reply Rpt. at ¶¶ 51, 57-58.) Like this Court had previously, she concluded it is not. Specifically, Ms. Lietzan explained how "premarket approval—the hallmark of the FDA regulatory framework for all medical products, including not only new drugs and biological products but many medical devices—is required specifically for (and granted specifically to) products that are manufactured, marketed, and sold in the market." (*Id.* at ¶ 51.) Ms. Lietzan went on to explain

[redacted]

[redacted]

(*Id.* at ¶ 58.) Ms. Lietzan's analysis is consistent with the safe harbor case law and the guidance from *Proveris* about how the requirement of FDA premarket approval is considered when finding an exception to the safe harbor. *See* 536 F.3d at 1265.

Ultimately, however, Ms. Sensabaugh and Ms. Lietzan do not disagree on the underlying facts—information about the cultured host cells is submitted to FDA as part of Sarepta's BLA application, but those cultured host cells are not the products that require FDA's premarket approval for Sarepta to sell. As a result, the question of whether the cultured host cells are subject to "FDA premarket approval" under *Proveris* and the cases following it is a legal one for the Court to decide. As the Court decided at the motion to dismiss stage, the cultured host cells are not a "patented invention" under 35 U.S.C. § 271(e)(1), and summary judgment that Sarepta's use of those cultured host cells is not protected by the safe harbor is appropriate.

c. The '617 Patent is Not Extendable Under Section 156

It is undisputed that the '617 patent is not subject to a term extension under Section 156. Section 156 permits a term extension for, among other things, a patent covering a product that "has been subject to a regulatory review period before its commercial marketing or use." 35 U.S.C. § 156(a)(4). The statute defines "product" as including "drug product," which means "the active ingredient" of a new drug or biological product. 35 U.S.C. § 156(f). In *Proveris*, after holding that the safe harbor was not applicable because the OSA was not subject to regulatory approval, the Federal Circuit also recognized that the patentee was "not eligible for the benefit of the patent term extension afforded by 35 U.S.C. § 156(f)." 536 F.3d at 1265-66. Because the cultured host cells claimed in the '617 patent are likewise not eligible for a patent

term extension under Section 156, the safe harbor does not apply. In fact, Sarepta's expert Ms. Sensabaugh failed to even consider whether Section 156 was applicable to the '617 patent, let alone how its applicability would affect Sarepta's safe harbor defense. (*See* Ex. 17, Sensabaugh Dep. Tr. at 32:15-17 ("Q: And in your work on this case, you did not do any analysis on patent term extension, correct? A: Correct.").) For this additional reason, there is no dispute of material fact bearing on the legal question of whether the safe harbor applies in this case, and summary judgment is warranted.

D. Conclusion

No dispute of material fact between the parties exists regarding whether the safe harbor is applicable in this case. To the extent there is any remaining question, that dispute is a dispute of law, ripe for resolution by the Court. The Court already correctly resolved this question at the motion to dismiss stage, and Plaintiffs therefore respectfully request that the Court grant their Motion for Summary Judgment.

IV. *DAUBERT* MOTION TO EXCLUDE DR. MARK KAY'S OPINIONS ON ENABLEMENT AND WRITTEN DESCRIPTION UNDER 35 U.S.C. § 112

Sarepta's expert's opinions on the enablement and written description requirements in 35 U.S.C. § 112 are based on a claim construction that this Court rejected. Those opinions should therefore be excluded.

Dr. Mark Kay, Sarepta's expert on a variety of invalidity issues, served his expert reports months after the claim construction proceedings in this case. During claim construction, Sarepta argued that the term "AAV . . . capsid protein" requires certain "functional properties," but the Court did not agree and construed the term to have its plain and ordinary meaning, as Plaintiffs advocated. (D.I. 91 at 56-74; D.I. 118.) Dr. Kay nonetheless based his enablement and written

description analyses on a construction of "AAV . . . capsid protein" that includes "functional properties" that Sarepta argued during claim construction were required.

Dr. Kay's enablement and written description opinions therefore should be excluded under Federal Rule of Evidence 702 as lacking "fit," which requires that an "expert's testimony must be relevant for the purposes of the case and must assist the trier of fact." *Schneider v. Fried*, 320 F.3d 396, 404 (3d Cir. 2003). Because his opinions are based on "functional properties" that the Court expressly declined to include it its construction, his analyses are not "relevant for the purposes of the case" and will not "assist the trier of fact." *Id.*

A. Summary of the Argument

1. During claim construction, Sarepta argued that, based on alleged prosecution disclaimer, the claim term "AAV . . . capsid protein" requires certain "functional properties." (D.I. 91 at 66.) Plaintiffs disagreed and argued there was no disclaimer, no such "functional properties" are required, and the term should have its plain and ordinary meaning. (D.I. 91 at 57-61.) The Court agreed with Plaintiffs and construed the term to have its plain and ordinary meaning, finding there was no "clear and unmistakable" disclaimer. (D.I. 118; Ex. 18, Claim Construction Tr. at 64:18-65:7.)

2. Months later, Dr. Mark Kay—Sarepta's expert on, among other issues, enablement and written description under 35 U.S.C. § 112—provided expert reports. In them, he offered a construction for "AAV . . . capsid protein" that requires certain "functional properties" that Sarepta argued during claim construction were required, but that the Court did not adopt in its construction.

3. Dr. Kay then opined that the asserted claims do not meet the enablement and written description requirements under his construction (i.e., not the Court's construction). As

such, Dr. Kay's enablement and written description opinions should be excluded under Federal Rule of Evidence 702 as lacking "fit."

B. Statement of Facts

i. The '617 Patent Covers Cultured Host Cells Encoding an "AAV . . . Capsid Protein"

The '617 patent claims cultured host cells "containing a recombinant nucleic acid molecule encoding an AAV . . . capsid protein[,]" along with other requirements. (Ex. 1, '617 patent at claims 1, 3, 5.)[1] The AAV capsid protein sequences in the recombinant nucleic acid molecules required by the claims, if expressed, can be used to form AAV capsid proteins. Those AAV capsid proteins, when put together in a particular ratio, can be used to form an AAV capsid. An AAV capsid is a hollow shell made of proteins, which can be manipulated so that the viral genome (or "DNA," "genetic material," or "nucleic acids") normally contained within the shells is replaced with bioengineered genetic material—i.e., desired genes. (*See* D.I. 20 at 3-4; Ex. 19, Leone Claim Construction Decl. at ¶ 45.) The resulting bioengineered AAVs—known as an AAV viral vector—can then be administered to patients and deliver the desired gene to the patients' cells. (*See* D.I. 20 at 3-4.)

ii. The Court Rejected Sarepta's Attempt to Insert a "Functional" Requirement into "AAV . . . Capsid Protein" at *Markman*

The difference between each of these constructs—cultured host cells containing recombinant nucleic acids encoding capsid proteins, capsid proteins, AAV capsids formed from

[1] Like the other asserted claims, asserted independent claim 7 of the '617 patent and its dependent claims require recombinant nucleic acid molecules containing certain sequences, but unlike the other asserted claims, these claims do not expressly require that those sequences encode "AAV . . . capsid proteins." Nonetheless, in his enablement and written description analyses, Dr. Kay applied the "functional" requirements that he opined are part of the term "AAV . . . capsid protein" to these claims. (Ex. 11, Kay Op. Rpt. at ¶123.) Moreover, in his expert reports, Dr. Kay did not separately analyze enablement and written description for each individual asserted claim, and instead analyzed all the asserted claims together.

capsid proteins, and AAV viral vectors including genetic material—are critical, as the Court recognized during the claim construction phase of this case. During claim construction, Sarepta argued that "AAV . . . capsid proteins" "require[] functional properties . . . for example, with respect to capsid formation, nucleic acid packaging, tropism, transduction efficiency, [and] . . . immunological activity." (D.I. 91 at 66.) Sarepta argued that such functional properties are required because of an alleged clear and unmistakable disclaimer of the full scope of "AAV . . . capsid proteins" during prosecution, relying on a declaration submitted to the Patent Office by inventor Dr. Jim Wilson during prosecution of a different patent with different claims. (D.I. 91 at 73-74.)

Plaintiffs disputed Sarepta's argument. As Plaintiffs explained, the word "functional" does not appear in the asserted claims to describe AAV capsid proteins. (D.I. 91 at 60.) That is not surprising, because as Plaintiffs also explained, none of the asserted claims require AAV capsid proteins, the fully-formed AAV capsid, or an AAV viral vector that includes a transgene capable of delivery to a patient. Instead, they require cultured host cells comprising recombinant nucleic acid molecules that contain nucleic acid sequences that encode AAV capsid proteins. (D.I. 91 at 57.) Plaintiffs further explained that to the extent the '617 patent's specification discusses particular functions AAV capsid proteins perform, importing those functionalities into the claims would be a "cardinal sin." (D.I. 91 at 59 (citing *SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1340 (Fed. Cir. 2001)).)

As to Dr. Wilson's declaration that Sarepta relied on, it is from the prosecution of a different patent with different claims. As Dr. Wilson's declaration explains, that declaration is limited to claims "claims which expressly recite that the AAV has an AAV7 capsid which has sequences packaged therein"—in other words, the AAV viral vector encoding a transgene. (D.I.

80-6, JA776-781 at JA780.) As Plaintiffs pointed out at the *Markman* hearing in this matter, the claims here are not to the AAV viral vector including the transgene, but instead covered "cultured host cells [that] simply have nucleic acid that encode the vp1. They're not the final gene therapy product." (Ex. 18, Claim Construction Tr. at 53:14-55:1.)

The Court construed "AAV . . . capsid protein" to have its plain and ordinary meaning, as Plaintiffs contended. (D.I. 118.) In doing so, the Court found there was no clear and unmistakable disclaimer requiring a particular function or functions, that the statements in Dr. Wilson's declaration were "just not all that clear and unmistakable," and that even if they had been, Dr. Wilson's statements would not "carry over to the present context." (Ex. 18, Claim Construction Tr. at 64:18-65:7.)

iii. Dr. Kay's Expert Report Improperly Requires "AAV . . . Capsid Protein" to Include Functions Rejected by the Court

In his expert reports, contrary to the construction adopted by the Court, Dr. Kay opined that the meaning of "AAV . . . capsid protein" is "a protein that is capable of forming a stable AAV capsid that can carry out minimal functions of packaging the viral genome and delivering the viral genome to a cell." (Ex. 11, Kay Op. Rpt. at ¶ 122; *id*. at ¶ 124 ("the term 'AAV capsid' requires a functional capsid protein").) Dr. Kay did this under the guise of defining the "plain and ordinary meaning" (i.e., the Court's construction) of "AAV . . . capsid protein." (*Id*. at ¶ 122.)

More problematic, Dr. Kay's construction includes "functional properties" that Sarepta argued were "required" during claim construction, but that the Court rejected. (*See* D.I. 91 at 66.) Broken down, Dr. Kay's construction requires "a protein that":

a) "is capable of forming a stable AAV capsid," that can "carry out" the "functions of"
b) "packaging the viral genome" and
c) "delivering the viral genome to a cell."

(Ex. 11, Kay Op. Rpt. at ¶ 122.) During claim construction, Sarepta argued the same "functional properties" were required, albeit using slightly different language. Sarepta argued that "AAV . . . capsid proteins":

a) "with respect to capsid formation" "require[] functional properties" including
b) "nucleic acid packaging," and
c) "transduction efficiency."[2]

(D.I. 91 at 66.) The Court refused to include any of these "functional properties" in its construction. (D.I. 118.)

In his expert reports, Dr. Kay opined that the asserted claims of the '617 patent do not meet the section 112 enablement and written description requirements, relying on his improper construction of "AAV . . . capsid protein," with its included "functional" aspects. (Ex. 20, Kay Reply Rpt. at ¶¶ 12-13). For example, for enablement, Dr. Kay opined that:

- "The specification provides no guidance as to how to select capsid protein sequences with functional characteristics such as encapsidation, viral genome packaging, tissue tropism, or serology, from the vast numbers of sequences in the claimed genera." (Ex. 11, Kay Op. Rpt. at ¶ 344.)

- "This quantity of work would be far too great . . . to test any of the other basic functions of an AAV virion, such as viral genome packaging capability, serology, tissue tropism, and transduction efficiency." (*Id*. at ¶ 358.)

- "The '617 patent provides no indication that, for example, any particular modification would allow the resulting protein to retain the ability to be part of a functional capsid, or any other functional characteristic, or whether the modification must be made in conjunction with other modifications to preserve that function of the protein, or any other function of the protein." (*Id*. at ¶ 360.)

Similarly, for written description, Dr. Kay opined in his expert reports that, for example:

- "This narrow disclosure is not sufficient to permit a person of ordinary skill in the art to recognize or visualize those AAV capsid sequences encompassed within the vast claimed genera that are capable of carrying out the most basic functions of an AAV capsid

[2] As Dr. Kay explained in his deposition, transduction is "the transfer of the gene of interest into the cell where it's expressed." (*See* Ex. 2, Kay Tr. at 49:25-50:6.)

protein, such as capsid formation or the packaging and delivery of nucleic acid molecules to target host cells." (*Id*. at ¶ 309.)

- "The specification does not contain sufficient disclosure to permit a person of ordinary skill in the art to recognize or visualize those AAV capsid sequences encompassed within the claimed genera that are capable of carrying out the most basic functions, such as the formation of AAV capsids." (*Id*. at ¶ 22.)

- "The absence of any discussion in the specification of the relation of particular sequence motifs to the functions of the encoded capsid proteins makes it impossible for a person of skill in the art, faced with the enormous number of claimed sequences, to distinguish those that might form a functional capsid from those that will not." (*Id*. at ¶ 311.)

In his deposition, Dr. Kay confirmed that he used his improper construction in his enablement and written description analyses. He testified that in paragraph 122 of his opening expert report, he opined that the meaning of AAV capsid protein is "a protein that is capable of forming a stable AAV capsid and can carry out minimal functions of packaging the viral genome and delivering the viral genome to a cell." (Ex. 2, Kay Tr. at 29:25-30:15.) He further confirmed that under his construction, the "stable capsid must be able to carry out two functions . . . packaging the viral genome and delivering the viral genome to a cell." (*Id.* at 34:6-15.) He then explained that he used his improper construction in paragraph 122 of his opening report in both his enablement and written description analyses:

> Q. So your—you have a definition in paragraph 122 . . . of "AAV capsid protein." Did you use that definition when you were doing your enablement analysis?
>
> A. Yes.
>
> Q. Okay. Did you use that definition in paragraph 122 of "AAV capsid protein" when you were doing your written description analysis that's in your expert reports?
>
> A. Yes.

(*Id.* at 42:16-43:4 (objection omitted); *see also id*. at 41:14-25, 45:2-12.)

C. Argument

1. Dr. Kay Applied a Construction that is Inconsistent with the Court's Construction

The construction of "AAV . . . capsid protein" that Dr. Kay applied in his enablement and written description opinions is wrong as both a legal and factual matter. Legally, his construction—requiring that the "stable capsid must be able to carry out two functions . . . packaging the viral genome and delivering the viral genome to a cell" (Ex. 2, Kay Tr. at 34:6-15)—includes functionalities Sarepta argued during claim construction were required. The Court, however, rejected Sarepta's argument and construed the term to have its "plain and ordinary meaning," as Plaintiffs argued. (D.I. 118.)

It is improper for Sarepta and its expert to now try and alter the Court's construction of "AAV . . . capsid protein," especially to include "functional properties" that the Court did not adopt in its construction. *Exergen Corp. v. Wal-Mart Stores, Inc.*, 575 F.3d 1312, 1321 (Fed. Cir. 2009) ("No party may contradict the court's construction to a jury"); *CytoLogix Corp. v. Ventana Med. Sys., Inc.,* 424 F.3d 1168, 1172 (Fed. Cir. 2005) ("The risk of confusing the jury is high when experts opine on claim construction before the jury even when, as here, the district court makes it clear to the jury that the district court's claim constructions control.").

The undisputed facts also demonstrate that Dr. Kay's "functional" construction is wrong. His construction requires "a protein that is capable of forming a stable AAV capsid" that can package a viral genome and deliver it to a cell. (Ex. 11, Kay Op. Rpt. at ¶ 122.) But Dr. Kay agrees with Plaintiffs' expert Dr. Leone that there are uses for empty AAV capsids—i.e., ones that do not have any packaged viral genome, and accordingly cannot "transfer" any "gene of interest into" a cell. (Ex. 2, Kay Tr. at 79:8-80:13; 49:25-50:6; Ex. 5, Leone Reb. Rpt. at ¶¶ 55, 393.) This is consistent with the language of the asserted claims, which does not exclude

sequences encoding AAV capsid proteins that are capable of forming empty AAV capsids. But Dr. Kay's construction would. Because his construction requires functions that the language of the claims does not require or support, it is factually incorrect. Had the inventors wished to include the functional properties included in Dr. Kay's construction, they could and would have made those requirements parts of the claims. *Int'l Rectifier Corp. v. IXYS Corp.*, 361 F.3d 1363, 1374 (Fed. Cir. 2004) ("Had the inventor meant 'adjacent,' he could have used that word.").

2. Because He Applied the Wrong Claim Construction, Dr. Kay's Opinions on Enablement and Written Description Should be Excluded under Rule 702

Because Dr. Kay's opinions on written description and enablement are based on an improper claim construction—rather than the Court's construction—his testimony on those topics should be excluded under Federal Rule of Evidence 702. Rule 702 reflects a "trilogy of restrictions on expert testimony: qualification, reliability and fit." *Schneider*, 320 F.3d at 404. Here, Dr. Kay's opinions do not meet the "fit" requirement, which requires that an "expert's testimony must be relevant for the purposes of the case and must assist the trier of fact." *Id.*; *see also* Fed. R. Evid. 702(d) (expert testimony is admissible only if "the expert has reliably applied the principles and methods to the facts of the case"). That is, Dr. Kay's written description and enablement analyses are not helpful for the Court or for the jury—and would likely confuse the latter—because they are not based on the Court's construction. Moreover, they are based on a construction that includes functionalities that the Court did not include in its construction, despite Sarepta's arguments during claim construction that those functionalities were required.

Courts consistently exclude or disregard expert testimony that is based on an improper claim construction. In *Liquid Dynamics Corp. v. Vaughan Co.*, 449 F.3d 1209, 1224 n.2 (Fed. Cir. 2006), the Federal Circuit affirmed the exclusion of expert testimony on enablement based on an impermissible construction, explaining that "[s]ince the enablement inquiry necessarily

depends on an interpretation of the claims, we conclude that the district court did not abuse its discretion in excluding the expert's testimony pertaining to enablement." And in *Frank's Casing Crew & Rental Tools Inc. v. PMR Techs., Ltd.*, 292 F.3d 1363, 1375 (Fed. Cir. 2002), the Federal Circuit disregarded testimony that used an overly stringent construction of "monitoring" in an infringement analysis, finding that under the correct reading of the term, the evidence was undisputed that all limitations were met. *See also Treehouse Avatar, LLC v. Valve Corp.*, 54 F.4th 709, 715 (Fed. Cir. 2022) ("We affirm that the grant of a motion to strike expert testimony is not improper when such testimony is based on a claim construction that is materially different from the construction adopted by the parties and the court."); *Cordis Corp. v. Boston Sci. Corp.*, 658 F.3d 1347, 1357-58 (Fed. Cir. 2011) (affirming the district court's disregard of expert testimony based on an incorrect understanding of the claim construction).

The same is true here. Dr. Kay applied a construction that is at odds with the Court's plain meaning construction of "AAV . . . capsid protein," and, in fact, a construction that includes "functional properties" Sarepta argued—but the Court rejected—during claim construction. Dr. Kay's enablement and written description opinions are premised on that incorrect construction, as Dr. Kay admitted at his deposition. (*See* Ex. 2, Kay Tr. at 45:2-12 (admitting that he used the construction set forth in his report for all his opinions).) The analysis in Dr. Kay's expert report makes the problem clear. For example, as part of his enablement opinion, he opined that the "quantity of work would be far too great . . . to test any of the other basic functions of an AAV virion, such as viral genome packaging capability, serology, tissue tropism, and transduction efficiency." (Ex. 11, Kay Op. Rpt. at ¶ 358; *see also supra* Section IV.B.3.) That is, his opinion on undue experimentation was premised on the experimentation required to determine if the claimed AAV capsid proteins perform functions that they are not

required to perform under the Court's construction. Thus, Dr. Kay's written description and enablement opinions should be excluded.

V. *DAUBERT* MOTION TO EXCLUDE MS. MULHERN'S TESTIMONY ON HOLD-UP

Sarepta's damages expert, Carla Mulhern, improperly and incorrectly characterized the damages analysis of Plaintiffs' expert, Dr. Randal Heeb, as "effectively capturing 'hold-up' value, rather than the intrinsic value of the '617 Patent." This is contrary to both the facts and the law. The concept of hold-up has never previously been applied outside of standard-essential-patent ("SEP") cases. And even applying the legal principles set out in those SEP cases, the facts here do not fit Ms. Mulhern's incorrect theory. She should not be permitted to present that theory to the jury.

A. Summary of the Argument

1. Here, there is no dispute that the '617 patent does not cover a standard essential technology, and no SEP issues exist in this case. Instead, the'617 patent covers cultured host cells that contain a recombinant nucleic acid molecule with a specific sequence encoding an AAV capsid protein. The '617 patent and asserted claims are not SEP claims where "hold-up" is a concern, nor do any facts in the record allow for that conclusion.

2. Even if hold-up did apply outside the SEP context, it is undisputed that Sarepta [redacted]. Under these facts, the concept of hold-up does not apply, and Ms. Mulhern's opinions to the contrary are not properly tied to the facts.

B. Factual Background

1. The Patented Technology

As discussed above, the '617 patent covers cultured host cells including a recombinant nucleic acid molecule that encodes the AAVrh.10 capsid protein and sequences at least 95% identical to AAVrh.10. *See supra* Sections II.B.1, III.B., and IV.B.1.

2. Ms. Mulhern's "Hold-Up" Allegations

In her expert report, Ms. Mulhern critiques the analysis of Plaintiffs' expert as capturing hold-up value rather than the value of the '617 patent. (Ex. 21, Mulhern Rpt. at ¶ 174 (stating that Dr. Heeb's analysis "is dependent upon a conceptually flawed bargaining framework that captures value beyond the intrinsic value of the '617 Patent due to hold-up[.]"; *see also id*. at ¶ 93 ("[I]n attributing the entirety of the value of Sarepta's development efforts during this 35-month period to the '617 Patent, Dr. Heeb is effectively capturing 'hold-up' value, rather than the intrinsic value of the '617 Patent."); *see also id*. at ¶¶ 94, 167-168, 304.) In launching this critique, Ms. Mulhern cites no instance of hold-up being applied outside of the SEP setting, and she admitted at her deposition that she was not aware of any such cases. (*See* Ex. 22, Mulhern Tr. at 104:15-105:2.)

Further, Ms. Mulhern admitted that early in development, Sarepta could have chosen to use technology outside the scope of the '617 patent (avoiding any hold-up), but chose not to. (*Id*. at 80:7-81:13, 112:4-12, 113:2-6.) Ms. Mulhern also admitted that [redacted] (*Id*. at 91:6-92:3.) Sarepta therefore had two approaches it could have taken to avoid the [redacted] it now faces, and expressly declined both paths.

C. Legal Standards

"Expert evidence can be both powerful and quite misleading because of the difficulty in evaluating it." *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 595 (1993). Gatekeeping for patent damages is particularly important "given the great financial incentive parties have to exploit the inherent imprecision in patent valuation." *Commonwealth Sci. & Indus. Rsch. Org. v. Cisco Sys., Inc.*, 809 F.3d 1295, 1301 (Fed. Cir. 2015). Rule 702 bars the testimony of an expert witness unless "[1] the testimony is based upon sufficient facts or data, [2] the testimony is the product of reliable principles and methods, and [3] the witness has applied the principles and methods reliably to the facts of the case." Fed. R. Evid. 702(b)-(d). In other words, the testimony must meet the three standards of qualification, reliability, and fit. "Fit" requires that an "expert's testimony must be relevant for the purposes of the case and must assist the trier of fact." *Schneider*, 320 F.3d at 404; *Fedorczyk v. Caribbean Cruise Lines, Ltd.*, 82 F.3d 69, 75 (3d Cir. 1996) ("An expert opinion is not admissible if the court concludes that an opinion based upon particular facts cannot be grounded upon those facts.").

D. Argument

Ms. Mulhern's opinions that Dr. Heeb's analysis improperly captures "hold-up" value are factually and legally unsound and should be excluded under Fed. R. Evid. 702. Permitting Sarepta to present Ms. Mulhern's opinions on hold up would only serve to confuse and mislead the jury regarding the relevant legal principles. Ms. Mulhern's opinions on hold-up should therefore be excluded.

1. "Hold-Up" Does Not Apply Outside of SEP Cases

Ms. Mulhern's hold-up opinions fail as a matter of law because hold up is only relevant in SEP cases. Courts in this district and around the country have found that hold-up "is a concept limited to the narrow situation where a patentee could demand a royalty in excess of a

reasonable royalty because a standard setting organization requires an entire industry to use patented technology to foster compatibility among devices." *Orexo AB v. Actavis Elizabeth LLC*, No. 17-0205-CFC, 2019 WL 10060475, at *2 (D. Del. Mar. 19, 2019) (quoting *Ericsson, Inc. v. D-Link Sys., Inc.*, 773 F.3d 1201, 1209 (Fed. Cir. 2014) ("Patent hold-up exists when the holder of a SEP demands excessive royalties after companies are *locked into using a standard*.") (emphasis added by court); *see also Astrazeneca AB v. Apotex Corp.*, 985 F. Supp. 2d 452, 501 (S.D.N.Y. 2013), *rev'd in part on other grounds sub nom. AstraZeneca AB v. Apotex Corp.*, 782 F.3d 1324 (Fed. Cir. 2015) (hold-up considerations are "simply inapplicable here, as the Patents do not cover a standard technology."); *cf. TCL Commc'n Tech. Holdings Ltd. v. Telefonaktiebolaget LM Ericsson*, 943 F.3d 1360, 1368 (Fed. Cir. 2019) ("hold-up . . . occurs when a patent-owner seeks to extract excessive value from its SEPs after the implementer is 'locked-in' to using the standard."). Here, the parties agree that the '617 patent is not a standard essential patent and no SEP issues exist in this case. (Ex. 22, Mulhern Tr. at 94:25-95:2; *see also id*. at 94:21-95:5; Ex. 23, Heeb Reply Rpt. at ¶¶ 60, 68 n.61.)

Outside of the SEP context, the Federal Circuit has found that it is appropriate to consider the delay a party would incur and the associated cost of that delay in assessing reasonable royalty damages, as Dr. Heeb has. Because "avoiding the patent would be difficult, expensive, and time-consuming, the amount the infringer would be willing to pay for a license is likely to be greater" later on in the process. *AstraZeneca*, 782 F.3d at 1335. In *AstraZeneca*, the Federal Circuit affirmed a district court's rejection of the same hold-up argument that Ms. Mulhern made here. The district court found that cases on hold-up "deal with the special situation in which a technical standard is set for an industry that puts one patent holder in a position to 'hold up' industry participants from implementing the standard," but that those "considerations are simply

inapplicable here, as the Patents do not cover a standard technology." *Astrazeneca*, 985 F. Supp. 2d at 501 (cleaned up). The same reasoning applies here, where there is no dispute that the '617 patent does not cover a standard technology.

Accordingly, Ms. Mulhern's hold up opinions should be excluded as unreliable, irrelevant (as they do not fit the facts of the case), and confusing and misleading to a jury. *See Orexo*, 2019 WL 10060475, at *2 (granting Daubert motion on "hold up" opinion that "ignores the facts at the time of the hypothetical negotiation and incorrectly applies Federal Circuit law").

2. "Hold-Up" Does Not Apply Because Sarepta [redacted]

Even if hold-up were applicable outside of SEP cases, Ms. Mulhern's hold-up opinions do not pass muster on the facts of this case. The relevant facts are undisputed. Before 2018, Sarepta was aware that the sequence of its AAVrh.74 vector that it uses in its products is nearly 99% identical to the sequence of AAVrh.10 claimed in the '617 patent family. (Ex. 14, Leone Reply Rpt. at ¶ 13; Ex. 24, REGENX0021629-53 at REGENX0021629.) [redacted]

[redacted] The '617 patent issued in January 2020. (Ex. 13, Leone Op. Rpt. at ¶ 58.) By that time, Sarepta's development was much further along, and it no longer had the option to choose a non-infringing alternative to the technology in the '617 Patent. (Ex. 22, Mulhern Tr. at 111:19-112:2.) Once the patent issued, [redacted] Sarepta moved ahead, knowingly infringing the claims of the '617 patent until it expired in November 2022. (Ex. 25, Heeb Corrected Op. Rpt. at ¶ 130.)

Even if hold-up was not limited to SEP cases, hold-up concerns themselves are inapplicable where, as here, Sarepta chose to continue development of its product in the face of the '617 patent, [redacted] *see also id*. at ¶¶ 57-91.) Ms. Mulhern does not address or refute this statement. In fact, Ms. Mulhern agreed at her deposition that [redacted] (Ex. 22, Mulhern Tr. at 91:6-92:3, 113:2-6.)

The facts here are undisputed—[redacted] That Sarepta faced either delay [redacted] does not lead to Ms. Mulhern's conclusion that there must be hold-up. *Astrazeneca*, 985 F. Supp. 2d at 501. On the contrary, delay and the resulting cost can be "one of the most salient features of the negotiating dynamic" leading to a reasonable royalty and "may not now be ignored." *Id.* at 501. In *Astrazeneca*, the district court found that the plaintiff had "shown through overwhelming evidence that it was in the driver's seat in the negotiations and would have required [defendant] to pay a hefty portion of its profits for a license." *Id*. at 502. The same is true here, where Sarepta's use of the patented technology in the development of its SRP-9001 product was anticipated to result in an estimated savings of [redacted] if Sarepta did not delay development. (*See, e.g.*, Ex. 25, Heeb Corrected Op. Rpt. at ¶ 18.)

For this additional reason, Ms. Mulhern's "hold up" opinions do not fit the facts of this case and should be excluded under *Daubert* and Fed. R. Evid. 702. 509 U.S. at 595.

Respectfully submitted,

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CERTIFICATE OF SERVICE

I HEREBY CERTIFY that on this 25th day of August, 2023, a copy **Plaintiffs' Motion for Summary Judgment of No Invalidity Under 35 U.S.C. § 101, Motion for Summary Judgment that Sarepta's Infringing Activities are Not Protected by the Safe Harbor of 35 U.S.C. § 271(e)(1), *Daubert* Motion to Preclude the Testimony of Dr. Mark Kay on Invalidity Under 35 U.S.C. § 112, and *Daubert* Motion to Preclude the Testimony of Carla Mulhern on Hold-Up** was caused to be sent via electronic mail to the following attorneys of record:

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